Intake of Flavonols and Flavones and Risk of Coronary Heart Disease in Male Smokers

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Flavonols and flavones are antioxidant polyphenolic compounds found in tea, vegetables, fruits, and wine. In experimental studies they have been effective free radical scavengers, metal chelators, and antithrombotic agents. In the few epidemiologic studies of these agents, some have suggested an inverse association between intake of flavonols and flavones and the risk of cardiovascular disease. Our study population comprised 25,372 male smokers, 50–69 years of age, with no previous myocardial infarction. They were participants of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, which was a randomized, double-blind, placebo-controlled trial with daily supplementation of alpha-tocopherol (50 mg per day) and/or beta-carotene (20 mg per day). The men completed a validated dietary questionnaire at baseline. After 6.1 years of follow-up, there were 1,122 nonfatal myocardial infarctions and 815 coronary deaths. In the multivariate model, the relative risk of nonfatal myocardial infarction was 0.77 (95% confidence interval = 0.64–0.93) among men in the highest (median 18 mg per day) compared with the lowest (median 4 mg per day) quintile of flavonol and flavone intake. The respective relative risk for coronary death was 0.89 (95% confidence interval = 0.71–1.11). Thus, intake of flavonols and flavones was inversely associated with nonfatal myocardial infarction, whereas there was a weaker association with coronary death. (Epidemiology 2001;12:62–67)

Keywords: antioxidants, coronary heart disease, flavonoids, diet.

Flavonols and flavones are antioxidant phenolic compounds found in vegetables, fruits, tea, and red wine. They are known to be effective scavengers of free radicals[1] and chelators of transitional metals (Fe, Cu) that catalyze free radical production.[2] They also reduce macrophage-mediated low-density lipoprotein oxidation.[3,4] Quercetin and apigenin have inhibited hemostasis *in vitro* but not in concentrations found in human plasma.[5,6] Under certain reaction conditions, flavonoids can also have pro-oxidant activity.[7,8]

Epidemiologic studies have not shown a consistent association between flavonoid intake and the risk of coronary heart disease. In three studies, flavonoids had an inverse association with coronary heart disease,[9–11] but the results of two other studies did not support these findings.[12,13] We investigated the associations between flavonol and flavone intake and the risk of nonfatal myocardial infarction and coronary death in a cohort of Finnish male smokers.

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The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study was supported by a contract from the U.S. National Cancer Institute (NO1-CN-45165).

Submitted November 29, 1999; final version accepted June 13, 2000.

Subjects and Methods

Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) was a double-blind, placebo-controlled primary prevention trial undertaken to determine whether supplementation with alpha-tocopherol, beta-carotene, or both would reduce the incidence of lung cancer in male smokers. The rationale, design, and methods of the study as well as the characteristics of the participants have been described in detail.[14]

The participants of the ATBC Study were male smokers recruited from the total male population 50–69 years of age in southwestern Finland (N = 290,406). To be eligible, they had to smoke at least five cigarettes per day at entry and to give written informed consent. The exclusion criteria included a history of cancer or other serious disease limiting long-term participation; use of vitamin E, vitamin A, or beta-carotene supplements in excess of predefined doses [vitamin E >20 mg per day, vitamin A >20,000 international units (4,000 retinol equivalents) per day, or beta-carotene >6 mg per day] and treatment with anticoagulant agents.

After these exclusions, 29,133 men were randomized into one of the four supplementation regimens: alpha-tocopherol alone (daily dose 50 mg), beta-carotene alone (20 mg), alpha-tocopherol and beta-carotene, or placebo. Follow-up continued for 5–8 years (median 6.1 years).

Diet was assessed at baseline using a self-administered, modified diet history questionnaire.[15] This questionnaire was satisfactorily completed by 27,111 participants (93%). In addition, 1,739 men reported a previous myocardial infarction diagnosed by a physician. Thus, 25,372 men were included in the present analyses.

Baseline Measurements

At baseline, the men completed a questionnaire on general background characteristics and medical and smoking histories. Height, weight, and blood pressure were measured, and serum samples were stored at −70°C. Serum total cholesterol and high-density lipoprotein cholesterol levels were determined enzymatically cholesterol oxidase-4-aminophenazone (CHOD-PAP) method, Boehringer Mannheim, Mannheim, Germany.

Dietary Assessment

The diet questionnaire included 276 food items and mixed dishes. It was used with a portion size picture booklet of 122 photographs of foods, each with three to five different portion sizes. The subject was asked to report the usual frequency of consumption and the usual portion size of foods during the previous 12 months. The frequencies were reported as the number of times per day, week, or month. At the first baseline visit, the questionnaire and the picture booklet were given to the subject to be completed at home. At the second baseline visit 2 weeks later, the questionnaire was returned and reviewed and completed with the help of a nurse.

The food consumption data were used to compute daily nutrient intake values based on the food composition database and related software at the National Public Health Institute. These data are based on chemical analyses of Finnish foods, with the exception of flavonol and flavone content, which is mainly based on composition analyses done by Hertog and colleagues.[16,17] The flavonol content of berries is, however, based on Finnish analyses.[18] Total flavonol and flavone intake was calculated as a sum of intakes of quercetin, kaempherol, myricetin, luteolin, and apigenin.

The dietary method was validated in a pilot study carried out among 190 men before the ATBC Study.[15] The men completed the questionnaire first and then kept 24 days of food records, spread over 6 months, as the reference method. They filled in the questionnaire again at the end. The energy-adjusted correlations between the first or the second dietary questionnaire and the food records were 0.59/0.66 for flavonols and flavones.

Ascertainment of Endpoints

The endpoints of this study were the first nonfatal myocardial infarction (alive on day 28 after the onset of the event) and death due to coronary heart disease (coronary death). Only the first of these events after randomization was registered as an endpoint. Endpoints were identified from national registers. In Finland, all hospitalizations are entered into the Hospital Discharge Register and all deaths into the Register of Causes of Death. Both registers use the codes of the *International Classification of Diseases* (the 8th revision was used through 1986 and the 9th revision thereafter).

Record linkage to the registers was done using the unique personal identification number. The first acute myocardial infarction (code 410) after randomization was searched for in the Hospital Discharge Register. When a case was found, survival beyond 28 days from the beginning of the attack was checked in the Register of Causes of Death, and the survivors were considered cases of nonfatal myocardial infarction. Coronary death cases were considered to be those who died within 28 days together with those fatal cases identified from the Register of Causes of Death with the underlying cause of death coded as 410–414. Register follow-up continued throughout the ATBC Study, and thus cases were also identified among dropouts. After 6.1 years of follow-up, there were 1,122 nonfatal myocardial infarctions and 815 coronary deaths.

Validity of the diagnoses of the coronary events in the registers has been evaluated; 94% of the cases of a random sample (N = 408) retained either definite or possible myocardial infarction in a review of clinical and autopsy data according to the FINMONICA criteria.[19]

Statistical Analysis

The participants contributed follow-up time from the date of randomization until first myocardial infarction, death, or end of trial (April 30, 1993). Men were grouped into quintiles of energy-adjusted intakes of flavonols and flavones and nutrients calculated from the food consumption data. Total flavonol and flavone intake and all nutrients were log-transformed before the energy adjustment, which was done by the regression residual method.[20] Alcohol intake was not energy adjusted.

Proportional hazards models were used to estimate the relative risks (RRs) and 95% confidence intervals (CIs) of coronary heart disease associated with intake of flavonols and flavones and selected foods, with simultaneous adjustment first for age and supplementation group and second for cardiovascular risk factors (systolic and diastolic blood pressure, serum total cholesterol, serum high-density lipoprotein cholesterol, body mass index, smoking years, number of cigarettes smoked daily, history of diabetes mellitus or coronary heart disease, marital status, education, and leisure-time physical activity).

TABLE 1. Relation of Energy-Adjusted Intake of Flavonols and Flavones to Selected Coronary Heart Disease Risk Factors and Intake of Nutrients and Foods at Baseline

	Quintile of Flavonol and Flavone Intake				
	1	2	3	4	5
Median intake of flavonoids, mg	3.94	6.01	8.01	10.8	17.8
Median of					
Age, years	57.7	57.4	56.8	56.8	56.8
Years smoked	38	37	36	35	35
No of cigarettes per day	20	20	20	20	20
Body mass index, kg/m^2	25.9	26.0	26.0	26.0	26.0
Serum total cholesterol, mmol/liter	6.19	6.20	6.21	6.14	6.08
Serum HDL cholesterol, mmol/liter	1.19	1.17	1.18	1.16	1.17
Systolic blood pressure, mmHg	140	140	140	140	140
Diastolic blood pressure, mmHg	88	88	88	88	88
Percentage of group					
Education (>11 years)	4.5	6.5	8.5	12.7	20.1
Leisure-time physical activity (≥3 times per week)	16.7	18.2	19.4	20.2	21.0
Wine drinkers [≥1 glass (120 ml)/week]	4	7	10	16	21
Tea drinkers [≥1 cup (170 ml)/week]	0	0	1	16	71
Median daily intake of					
Energy, kcal	2,672	2,703	2,760	2,777	2,689
Total fat, gm	120	119	119	118	112
Fiber, gm	21.4	23.4	24.8	26.0	25.1
Saturated fatty acids, gm	53	52	49.9	47.9	44.3
Monounsaturated fatty acids, gm	35	35	35.3	35.2	30.1
Polyunsaturated fatty acids, gm	8.8	9.6	10.2	10.9	11.0
Trans-saturated fatty acids, gm	3.0	3.0	3.0	3.0	2.9
Cholesterol, mg	533	542	553	551	519
Alcohol, gm	11.6	11.3	10.7	11.0	10.8
Beta-carotene, μg	1,127	1,520	1,842	2,163	2,200
Vitamin C, mg	59.5	79.5	95.0	110	109
Vitamin E, mg	9.1	10.1	10.9	11.6	11.8
Median daily consumption of					
Fruits, gm	28	55	79	102	102
Berries, gm	12	22	31	39	37
Vegetables, gm	55	81	102	121	128

HDL = high-density lipoprotein.

Results

The median intake of flavonols and flavones was 8.0 mg per day. There was more than a fourfold difference in the median flavonol and flavone intake between the highest and the lowest quintiles of energy adjusted intake (Table 1). Men who had the highest intake of flavonols and flavones were more educated; were physically more active; were more often wine or tea drinkers; and ate more fruits, berries, and vegetables than those with low intake of flavonols and flavones. In addition, men with high intake of flavonols and flavones had higher intake of polyunsaturated fatty acids, beta-carotene, vitamin C, and vitamin E and lower intake of saturated fatty acids than men with low intake of flavonols and flavones.

Correlations between intakes of flavonols and flavones and nutrients are shown in Table 2. The highest correlation was with vitamin C ($r = 0.50$). The highest correlations between flavonol and flavone intake and consumption of foods rich in flavonols and flavones were tea ($r = 0.63$) and vegetables ($r = 0.44$).

Flavonol and flavone intake was associated with the risk of nonfatal myocardial infarction (Table 3). After adjustment for age and supplementation group, the RR of nonfatal infarction among men in the highest compared with the lowest quintile of flavonol and flavone intake was 0.77 (95% CI = 0.64–0.93). In the multivariate model adjusting further for cardiovascular risk factors, the RR was unchanged (RR = 0.77, 95% CI = 0.64–0.93). When subjects reporting coronary heart

TABLE 2. Energy-Adjusted Correlations among Flavonols and Flavones, Foods Rich in Flavonols and Flavones, and Selected Nutrients

	Flavonols and Flavones	Vegetables	Fruits	Berries	Tea	Wine
Flavonols and flavones	1.00	0.44	0.36	0.32	0.63	0.23
Fiber	0.18	0.20	0.22	0.21	0.01	0.13
Alcohol	−0.00	0.09	−0.06	−0.15	0.05	0.24
Vitamin C	0.50	0.62	0.56	0.48	0.11	0.14
Vitamin E	0.23	0.33	0.19	0.11	0.10	0.12
Beta-carotene	0.35	0.61	0.30	0.28	0.12	0.13

TABLE 3. Relative Risk (RR) 95% CI of Nonfatal Myocardial Infarction (MI) and Coronary Death by Quintile of Energy-Adjusted Intake of Flavonols and Flavones

	Quintile of Flavonol and Flavone Intake				
	1	2	3	4	5
Person-years	28,484	28,917	29,289	29,514	29,697
Number of nonfatal MI cases	257	221	238	203	203
RR of nonfatal MI, age-adjusted (95% CI)	1.00	0.85 (0.71–1.02)	0.91 (0.77–1.09)	0.78 (0.65–0.94)	0.77 (0.64–0.93)
RR of nonfatal MI, multivariate* (95% CI)	1.00	0.84 (0.70–1.00)	0.89 (0.74–1.06)	0.77 (0.64–0.93)	0.77 (0.64–0.93)
Number of coronary deaths	191	151	172	150	151
RR of coronary death, age-adjusted (95% CI)	1.00	0.79 (0.64–0.98)	0.90 (0.74–1.11)	0.79 (0.64–0.98)	0.79 (0.63–0.97)
RR of coronary death, multivariate* (95% CI)	1.00	0.84 (0.68–1.04)	0.97 (0.79–1.20)	0.90 (0.73–1.12)	0.89 (0.71–1.11)

* Adjusted for age, supplementation group, systolic and diastolic blood pressure, serum total cholesterol, serum high-density lipoprotein cholesterol, body mass index, smoking years, number of cigarettes smoked daily, history of diabetes mellitus or coronary heart disease, marital status, educational level, and physical activity.

disease or diabetes mellitus at baseline were excluded, the risk of nonfatal myocardial infarction was similar (RR = 0.80, 95% CI = 0.65–0.99).

High intake of flavonol and flavones was associated also with lowered risk of coronary death in the base model (RR in the highest *vs* the lowest quintile of intake = 0.79, 95% CI = 0.63–0.97). After adjusting further for cardiovascular risk factors, however, this association was attenuated (RR = 0.89, 95% CI = 0.71–1.11).

In the food group analyses, consumption of wine was inversely related to the risk of coronary heart disease in the multivariate model (Table 4). Those who drank at least one glass of wine per week had decreased RR of coronary death (RR = 0.71, 95% CI = 0.55–0.93) compared with those who drank less than one glass of wine per week. There was also an inverse association for nonfatal myocardial infarction (RR = 0.77, 95% CI = 0.62–0.95). After further adjustment for total alcohol intake, the association between wine consumption and the risk of nonfatal myocardial infarction was attenuated markedly (RR = 0.89, 95% CI = 0.72–1.11). The risk of coronary death was attenuated only marginally, however (RR = 0.73, 95% CI = 0.55–0.95).

In addition, those in the highest quintile of vegetable consumption had lower risk of nonfatal myocardial infarction and coronary death than those in the lowest quintile (RR = 0.77, 95% CI = 0.63–0.94, and RR =

TABLE 4. Relative Risk (RR) of Nonfatal Myocardial Infarction (MI) and Coronary Death by Group of Intake of Foods Rich in Flavonols and Flavones

	Median Intake of Flavonols and Flavones (mg/day)	Person-Years	Nonfatal MI			Coronary Death		
			No. of Cases	RR	95% CI	No. of Cases	RR	95% CI
Fruits, gm/day*								
1st quintile, <25	5.1	28,739	239	1.00		189	1.00	
2nd quintile, 25–53	6.7	29,122	230	0.97	0.80–1.16	155	0.87	0.71–1.08
3rd quintile, 54–88	8.0	29,321	221	0.91	0.75–1.09	165	0.93	0.76–1.15
4th quintile, 89–136	9.1	29,307	219	0.89	0.74–1.08	157	0.90	0.73–1.12
5th quintile, >136	11.8	29,412	213	0.87	0.72–1.05	149	0.87	0.70–1.08
Berries, gm/day*								
1st quintile, <9	5.3	29,005	212	1.00		192	1.00	
2nd quintile, 9–19	6.6	29,021	226	1.07	0.89–1.29	167	0.96	0.79–1.20
3rd quintile, 20–33	7.7	29,209	233	1.11	0.92–1.34	166	0.98	0.79–1.21
4th quintile, 34–56	9.0	29,351	226	1.07	0.88–1.29	137	0.81	0.65–1.01
5th quintile, >56	11.6	29,314	225	1.05	0.87–1.27	153	0.91	0.73–1.13
Vegetables, gm/day*								
1st quintile, <52	5.0	28,387	239	1.00		202	1.00	
2nd quintile, 52–80	6.8	28,730	230	0.96	0.80–1.15	191	1.03	0.84–1.26
3rd quintile, 81–110	7.9	29,152	219	0.90	0.75–1.08	151	0.83	0.67–1.03
4th quintile, 111–156	9.3	29,473	244	1.01	0.84–1.22	150	0.86	0.69–1.07
5th quintile, >156	11.8	30,158	190	0.77	0.63–0.94	121	0.68	0.50–0.95
Tea*								
Less than one cup (170 ml)/day	7.1	119,850	937	1.00		665	1.00	
At least one cup/day	17.4	26,051	185	0.94	0.81–1.11	150	1.09	0.91–1.30
Wine†								
Less than one glass (120 ml)/week	7.7	128,359	1,021	1.00		752	1.00	
At least one glass/week	10.8	17,542	101	0.77	0.62–0.95	63	0.71	0.55–0.93

* Adjusted for age, supplementation group, systolic and diastolic blood pressure, serum total cholesterol, serum high-density lipoprotein cholesterol, body mass index, smoking years, number of cigarettes smoked daily, histories of diabetes mellitus and coronary heart disease, marital status, education, and leisure-time physical activity.
† Adjusted for age, supplementation group, serum total cholesterol, body mass index, smoking years, number of cigarettes smoked daily, histories of diabetes mellitus and coronary heart disease, marital status, education, and leisure-time physical activity.

0.68, 95% CI = 0.50–0.95, respectively). After adjusting further for flavonol and flavone intake, the association between vegetable consumption and nonfatal myocardial infarction was attenuated (RR = 0.84, 95% CI = 0.68–1.04); the same was true for coronary death (RR = 0.64, 95% CI = 0.46–0.91). Consumption of fruits, berries, or tea had little association with the risk of coronary heart disease. In a multivariate model that included simultaneously all foods (fruits, berries, vegetables, tea, and wine), RRs and their CIs were essentially the same as they were in the individual models of the foods.

Discussion

In this large cohort of male smokers, we observed an inverse association between flavonol and flavone intake and the risk of nonfatal myocardial infarction, with a much more modest association with coronary death.

In a Dutch cohort of 805 older men with coronary deaths during 5-year follow-up, a strong inverse relation between the intake of flavonols and flavones and the risk of coronary death was found (RR in the highest *vs* lowest tertile of intake = 0.32, 95% CI = 0.15–0.71).[9] Among those 693 men with no history of myocardial infarction at baseline, the RR of nonfatal and fatal myocardial infarction (N = 38) was attenuated (RR = 0.52, 95% CI = 0.22–1.23), whereas the risk of coronary death (N = 20) remained similar (RR = 0.29, 95% CI = 0.09–0.93). In a Finnish cohort of 5,133 men and women followed for 25 years, an inverse association between intake of flavonols and flavones and the risk of coronary death was observed among men (N = 324; RR in the highest *vs* lowest quartile of intake = 0.67, 95% CI = 0.44–1.00) and women (N = 149; RR = 0.73, 95% CI = 0.41–1.32).[10]

The largest cohort (51,529 men) in which associations between the intake of flavonols and flavones and the risk of coronary events have been studied so far is The Health Professionals Follow-Up Study.[13] During 6 years of follow-up there were 496 first nonfatal myocardial infarctions, among which there was a small positive association with the intake of flavonols and flavones (RR in the highest *vs* lowest quintile of intake = 1.08, 95% CI = 0.81–1.43). Among 4,814 men with coronary heart disease at baseline, there was an inverse association between flavonol and flavone intake and the risk of coronary death (RR = 0.63, 95% CI = 0.33–1.20). In the Caerphilly study of 1,900 Welsh men without previous myocardial infarction who were followed up for 14 years, 186 men were diagnosed with ischemic heart disease during the follow-up and 131 died from ischemic heart disease.[12] The intake of flavonols was not related to ischemic heart disease incidence (RR in the highest *vs* with lowest quartile of intake = 1.0, 95% CI = 0.6–1.6) but was positively associated with coronary mortality (RR = 1.6, 95% CI = 0.9- 2.9). The authors suggested that this association could be explained by high tea consumption, which in turn is related to a less healthful life-style and lower social class in the United Kingdom, in contrast to other populations in which high tea consumption is associated with a more healthful life-style. In a recent cohort study 34,492 postmenopausal women were followed for 10 years during which 438 deaths from coronary heart disease occurred.[11] The risk of coronary death was inversely associated with flavonoid intake (RR in the highest *vs* lowest quintile of intake = 0.62, 95% CI = 0.44–0.87).

Thus, most studies support a modest inverse association between the intake of flavonols and flavones and the risk of death from coronary heart disease, whereas no such association is evident for nonfatal myocardial infarction. We, however, found an inverse moderate association between flavonoid intake and risk of nonfatal myocardial infarction but only a weak association with coronary death.

The discrepant findings between our results and those of other studies may be due to different study populations. The intake of flavonols and flavones in our cohort was lower than in any of the previously reported cohorts, except for the other Finnish cohort.[10] The mean intake of flavonols and flavones was only 9.9 mg per day in our study, whereas in the previous studies the average intake has varied from 20[13] to 26[9] mg per day. The main reason for the low intake of flavonols and flavones is low consumption of tea and wine in Finland. On the other hand, all subjects in our study were male smokers, whereas other studies have also included women and the proportion of smokers has varied from 10% to 50%. It is possible that the effects of flavonoids are different between smokers and nonsmokers.

Flavonols and flavones have actions that could influence the risk of coronary heart disease. In *in vitro* studies they have inhibited the oxidation of low-density lipoprotein, which is considered an essential event in the development of atherosclerosis. Thus, flavonols and flavones could retard the progression of atherosclerosis. *In vitro* studies have indicated antithrombotic effects[5] that may be protective against thrombosis formation in the acute phase of myocardial infarction. Only a fraction of coronary deaths are caused by acute thrombosis in the coronary arteries, and so far there is no evidence that flavonols and flavones could influence other mechanisms of coronary death.

We found that men drinking on average one glass of wine weekly had lower risk of nonfatal myocardial infarction and coronary death than other men. This risk reduction was, however, unlikely to be due to flavonols and flavones,[21] because the difference in the total intake of flavonols and flavones was only 3 mg per day between the groups. The most likely explanation is differences in life-style factors. Wine drinkers are a very specific group of people in Finland; they are much more educated and urban than those who do not drink wine. Thus, although several background factors were taken into account in the effect estimates, some residual confounding probably remained. This interpretation is supported by our finding that the inverse association between wine consumption and the risk of nonfatal myocardial infarction was markedly attenuated after adjusting for alcohol intake.

Many studies have observed an inverse association between the consumption of vegetables and the risk of cardiovascular diseases. We also found lowered risk of nonfatal myocardial infarction and coronary death in the highest quintile of vegetable consumption. It is clear, however, that flavonols and flavones cannot explain our finding. First, the effect estimates were little changed when the intake of flavonols and flavones were simultaneously added to the model. Secondly, the difference in the median intake of flavonols and flavones was 6.7 mg per day between the highest and the lowest quintiles of vegetable consumption. A similar difference in flavonol and flavone intake was observed between the highest and the lowest quintiles of consumption of fruits and berries, but little difference in coronary risk was evident. Thus, other compounds in vegetables, such as carotenoids, vitamin C, potassium, magnesium, or dietary fiber, may be the true factors behind the inverse association with vegetable consumption. Similarly, men drinking on average one cup of tea daily had 10 mg per day higher intake of flavonols and flavones than those drinking less tea, but once again little difference was evident in coronary risk.

The largest decrease in coronary risk in our data was observed between the lowest and second-lowest quintiles of flavonol and flavone intake; differences among the four highest quintiles of intake were small. This pattern may indicate that only very low intake of flavonols and flavones increases the risk of coronary heart disease or that low intake is a surrogate measure for life-style risk factors related to the risk of coronary heart disease.

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